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Comparative Study of Intravenous Esmolol & Magnesium Sulphate in Attenuating Hemodynamic Response during Laryngoscopy & Endotracheal Intubation in Patients Undergoing Valvular Heart Surgery: a Randomised Clinical Trial -

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ABSTRACT

The present study aimed to compare the effectiveness of esmolol & magnesium sulphate in attenuating the hemodynamic response to endotracheal intubation and to note any significant side effects caused by these drugs.

Background: Induction with endotracheal intubation in patients undergoing valvular heart replacement pose lot of hemodynamic variations. Obtunding hemodynamic response which can be deleterious in such patients pose a challenge to the cardiac anaesthetist. We hypothesized that using esmolol as compared to magnesium sulphate will attenuate the hemodynamic response during laryngoscopy & endotracheal intubation in patients undergoing valvular heart replacement.

Methods: This was a double blind, randomised, single centre, interventional, prospective study. In this study 96 patients were divided into two groups with 48 patients each (n = 48) by sealed enveloped method of randomisation. Group E received esmolol 1.5 mg/ kg i.v and Group M received magnesium sulphate 50 mg/ kg i.v each diluted in normal saline to make up a volume of 50 ml & given via infusion slowly over 5 minutes by a burette set. Hemodynamic parameters like Heart Rate (HR), Mean Arterial Pressure (MAP), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) at baseline, 5 minutes after premedication, just before intubation 3, 5, 10 & 15 minutes post intubation were recorded. The last observation at the end of 15 minutes post intubation was considered as the end of study.

Results: All the enrolled patients were analyzed. The esmolol group showed a decrease in the H.R from baseline (86.13 ± 15.87) as compared to magnesium sulphate (98.51 ± 16.81 with a 95% CI, 4.62-4.69, *p* value < 0.001) 5 minute after premedication. There was statistically significant difference in H.R between both groups 5 minutes after drug administration.

Conclusion: Administration of esmolol before intubation in valvular heart patients undergoing valve replacement surgery controls the hemodynamic response much better as compared to magnesium sulphate.

Keywords: Esmolol; Hemodynamic response; Magnesium sulphate; Valvular heart replacement

INTRODUCTION

Laryngoscopy & tracheal intubation are usually always associated with a marked sympathetic response resulting in an increase in heart rate, blood pressure & arrhythmias. It has been shown since long that endotracheal intubation irritates the respiratory tract followed by reflex effect upon the heart [1]. It has both a sympathetic & parasympathetic effect. The maximal pressure response occurs with 10 seconds after the endotracheal tube placement [2]. This reflex is a vasovagal & cannot be corroborated as the nerve endings in the larynx & trachea are of the afferent portions of such a reflex.

Vagus nerve trunk consists of mixed fibres. The sympathetic response is a polysynaptic pathway with glossopharyngeal & vagus nerve forming the afferent arc. The response results from increased firing of the cardio-accelerator fibres and release of nor-epinephrine, epinephrine & vasopressin [3].

This response is variable, transient, unpredictable & are well tolerated in ASA I & II group of patients, but are of concern in patients having coronary artery disease, valvular heart disease, hypertension & cerebral pathologies with increased intracranial pressure as it may cause arrhythmias, myocardial ischemia & cerebral haemorrhage [4,5].

The ECG changes abnormalities produced immediately after intubation are sinus tachycardia, premature ventricular contractions with bigeminy or a trigeminal rhythm, decreased voltage of T waves, sinus bradycardia, increased PR interval, ST depression, VT & auricular fibrillation [6].

The damaged myocardium in cardiac disease patients will not tolerate these changes. Various non pharmacological & pharmacological agents have been used to decrease these response. In the non pharmacological response deeper plane of anaesthesia and LMA are used [7]. In the pharmacological agents used are lidocaine, opioids, droperidol, propranolol, nitroglycerine, calcium channel blocker, esmolol, fentanyl, magnesium sulphate, nifedipine, clonidine, gabapentin & dexmedetomidine.

Magnesium inhibits catecholamine release from adrenergic terminals & adrenal medulla during laryngoscopy and endotracheal intubation [8]. Esmolol is a potent ultrashort acting cardioselective beta1 adrenoceptor competitive antagonist. Its effect in lowering blood pressure is less as compared to heart rate [9].

In our study we have compared the effects of Esmolol 1.5 mg/kg body weight and Magnesium sulphate 50 mg/kg in patients during laryngoscopy and tracheal intubation in patients of valvular heart disease undergoing valve replacement.

METHODOLOGY

Study design & setting

This study was done in a tertiary care centre hospital based, prospective, randomised double-blind, interventional clinical trial conducted on patients undergoing valvular heart surgery under general anaesthesia in our institution & attached group of hospitals, after approval of the institutional ethical committee from April 2017 to October 2017. The study was doubly blinded i.e. the doctor giving anesthesia to the patient & the person collecting the data were not aware of as to which drug was given via infusion in a burette since both the drugs Esmolol and Magnesium are transparent and were prepared in saline and volume made up to 50 ml separately. This infusion was infused intravenously slowly over 5 minutes before induction of anesthesia. The trial was planned in such a way that neither the doctor nor the participant were aware of the group allocation and the drug received. The study drug was prepared by another anesthetist and after completion of the procedure & data collection the name was disclosed.

Written informed consent was obtained from all patients. Patients with ASA grade 3 & 4, of either sex, in the age group 20-55 yrs weighing from 40-79 kg and not allergic to study groups were included in the study. Patients having major organ dysfunction, on medications like hypnotics, narcotics analgesics, alpha 2 agonists, calcium channel blockers, and with difficult intubation were excluded from the study.

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Sample size

The sample size was calculated 48 in each group at alpha error 0.05 and power 80% assuming standard deviation of 10.05 in heart rate at 5 minutes after intubation as observed in study for minimal detectable difference of 5.86 per minute. The total sample size included 96 cases. The trial was planned in such a way that neither the doctor nor the participant were aware of the group allocation & the drug received. Study drug was prepared by another anaesthetist and after completion of the procedure the name was disclosed and data collected.

Intervention

Patients were randomly allocated into two groups of 48 patients in each. Randomisation was done by sealed envelope method. The randomization procedure which was adopted was of closed sealed envelope method. In this anesthetists were given randomly sealed opaque envelopes. After the patient consent to enter the trial was obtained an envelope was opened and the patient was then offered the allocated treatment regime. Study drugs were prepared and given by another anaesthetist.

Pre-operative & intraoperative management

The patients involved in this study compromised of patients having rheumatic heart disease undergoing valvular heart replacement surgery either aortic valve replacement or mitral valve replacement or both.

All the patients were visited one day prior to surgery & explained about the anaesthetic technique. Pre Anaesthetic Check-up (PAC) for each patient included any significant present/ past medical/ surgical history. Physical examination/ airway assessment, vital parameters, B.P/ pulse/ R.R. Routine investigation like Hb, TLC, DLC, LFT, RFT, ECG, X-ray chest (PA view), fasting and random blood sugar, platelet count, B.T, C.T, P.T, INR, S. electrolytes, & echocardiography.

Patients were given Morphine 0.1 mg/kg I.M and Diazepam 5 mg orally a night before surgery. On arrival in the O.T fasting status, written informed consent and PAC were checked. All the routine monitors were attached & the pre-op baseline vitals i.e. HR, SBP, DBP, MAP, SPO2 & ECG were taken.

Data were collected 5 min after pre-medication just prior to injection of drug. Study drug esmolol (1.5 mg/ kg i.v) or magnesium sulphate (50 mg/kg i.v) were diluted with normal saline to make a total volume of 50 ml & infused iv slowly over 5 minutes in double blind fashion. Patients were pre-oxygenated with 100% oxygen for 3 minutes. Induction was done with Inj. Midazolam 0.5 mg/kg I.V, fentanyl 2 microgram/kg, inj. etomidate 0.3 mg/kg i.v slowly over a period of 60-90 seconds until there was a loss of eyelash reflex. Inj. rocuronium 0.9 mg/ kg I.V was given to facilitate laryngoscopy and intubation. Data was collected at 1, 3, 5, 10 & 15 minutes after intubation. Surgery was allowed to commence after 15 minutes of intubation & anaesthesia maintained with 100% O_2, 1% Isoflurane, Inj. midazolam, inj. fentanyl, & inj. vecuronium bromide I.V. After the end of surgery patients were shifted to ICU for post op ventilation.

We considered the following parameters for our study:-

- Hypotension was defined as SBP < 25% of baseline value or 90 mm Hg, whichever was lower
- Hypertension was defined as SBP > 25% of baseline value as 150 mmHg whichever was higher
- Tachycardia was defined as HR > 25% of baseline value
- Bradycardia was defined as HR < 60 b/min. We chose the cut off values as 25% because of the fact that the patients would then require interventions as either volume replacement or inotropic support

Any episode of hypotension was managed by I.V fluid administration & inotropic support. While bradycardia was managed with atropine & Isoprenaline. If these episodes occurred during study period (within 15 minutes of intubation) appropriate management or intervention was done & the case was excluded from the study.

Statistical analysis

All the data were entered on excel sheet MS office Excel-2010 and analysed statistically using SPSS statistical software (ver 18.0.0) & XL stat. All the quantitative data were summarized in the form of mean ± SD. The difference between mean values of the two groups were analyzed using ANOVA one way test and within groups using paired T- test. All the qualitative data were summarized in the form of proportion. The difference between proportions were analyzed using chi-square test. The levels of significance and alpha error were kept 95% & 5% respectively, for all statistical analysis. *p* values < 0.05 were considered as Significant (S) & *p* value > 0.05 as statistically Non Significant (NS).

RESULTS

The two groups were compared demographically without any significant difference.

Baseline parameters were compared between the two groups. There was no significant difference between the two groups (*p* value > 0.05) as shown in table 1.

Heart Rate (HR)

The mean baseline H.R in group E was 98.02 ± S.D 19.31 and 94.49 bpm with a S.D of 16.49 in group M (*p* value = 3.449), 95% C.I 5.59-4.66 as shown in table 2 and table 3. H.R tended to decrease in group E than group M after 5 min of pre-medication which was statistically significant (*p* value < 0.05 with a 95% CI, 4.62-4.69) as shown in table 3. It remained decreased just before intubation in group E as compared to group M (*p* value < 0.05 with 95% CI 4.73-4.62). H.R was elevated more in group M as compared to group E at 1, 3 & 5 minutes post intubation with a *p* value of 0.04, 0.03 & 0.22 with 95% CI of 5.90-5.20, 5.95-5.15 & 5.18-6.22 respectively as shown in table 3.

There was a significant difference in both groups in H.R at 1, 3 &

Table 1: Demographic variables in both the groups

Variables	GROUP E		GROUP M		P value
	Mean	S.D	Mean	S.D	
Age (yrs)	35.44	10.47	35.60	11.92	0.947 NS
Wt (kg)	52.20	7.29	50.44	7.30	0.256 NS
Sex (M)	15		21		0.205 NS
(F)	33		27		
ASA Grade-3	35		33		0.653
Grade-4	13		15		
Mean duration of surgery	152.29		154.91	13.52	0.477

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Table 2: Comparison of mean baseline parameters.

	Baseline HR (per min)	Baseline SBP (mmHg)	Baseline DBP (mmHg)	Baseline MAP (mmHg)	Baseline SpO_2(%)
Group E	98.02 ± 19.31	134.47 ± 14.80	79.53 ± 11.29	98.00 ± 9.72	98.89 ± 1.03
Group M	94.49 ± 16.49	131.49 ± 11.97	78.16 ± 10.15	95.56 ± 8.78	98.76 ± 1.28
P value	0.353	0.296	0.544	0.213	0.587
Significance	**NS**	**NS**	**NS**	**NS**	**NS**

Table 3: Mean heart rate at various time intervals.

	Group E		Group M		P value	95% CI
	Mean (per min)	SD	Mean (per min)	SD		
Baseline	98.02	19.31	94.49	16.49	3.949	5.59-4.66
5 minute after premedication	86.13	15.87	98.51	16.81	0.0005	4.62-4.69
Just before Intubation	88.31	16.17	98.11	16.22	0.005	4.73-4.62
1 minute post intubation	100.67	19.74	108.64	18.40	0.049	5.90-5.20
3 minute post intubation	100.76	20.29	109.12	18.40	0.038	5.95-5.15
5 minute post intubation	99.18	17.41	104.31	22.11	0.224	5.18-6.22
10 minute post intubation	94.69	15.71	99.16	19.07	0.228	4.69-5.35
15 minute post intubation	94.07	14.06	96.20	18.16	0.534	4.15-5.10

Mean heart rate of patients at different intervals in both the groups is tabulated above.

5 min post intubation. Mean H.R after 10 & 15 min after intubation was below baseline value in Gp E than Gp M but statistically not significant.

Systolic Blood Pressure (SBP)

SBP of patients at different interval was compared with student t test. Baseline SBP in group E was 134 ± 14.80 & in group Gp M 131 ± 11.97 without any significant difference *p* value = 0.296 as shown in table 2. After study drug administration SBP was decreased in both the groups as shown in figure 1, which was statistically not significant (*p* value > 0.05).

Diastolic Blood Pressure (DBP)

Baseline DBP in GpE was 79.53 ± 11.29 & in Gp M 78.16 ± 10.15. After study drug administration DBP was decreased in both group. But the decrease was more in Gp M which was not statistically significant *p* value > 0.05. After intubation DBP rose post intubation in both the groups, but was more in group E, but statistically insignificant with a *p* value > 0.05. It rose at 3, 5, 10, & 15 min post intubation without any statistical significance as shown in the figure 2.

Mean Arterial Pressure (MAP)

MAP decreased in both groups in GpE from baseline (table 2) 98.09 ± 9.72 to 87.16 ± 9.65 and in Gp M 95.56 ± 7.78 to 84.12 ± 10.89 which was not significant statistically.(*p* value = 0.151). Gp M showed a decrease in the MAP after 1 and 3 minutes post intubation as compared to Gp E as shown in figure 3. There was no significant difference between the MAP in both the Groups after 5, 10, 15 min intubation. The MAP did not reach the baseline value upto 15 min of study duration from the time of pre-medication as shown in figure 3.

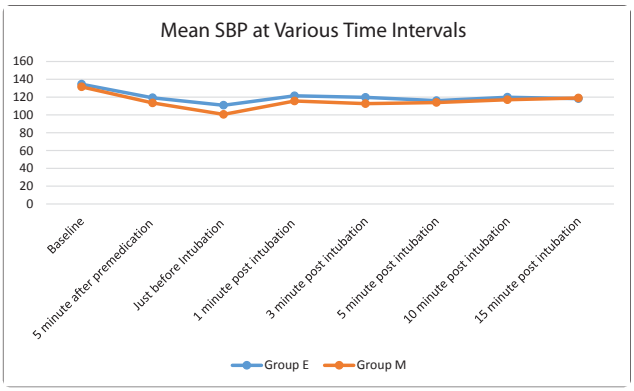

Figure 1: Mean SBP at various time intervals.

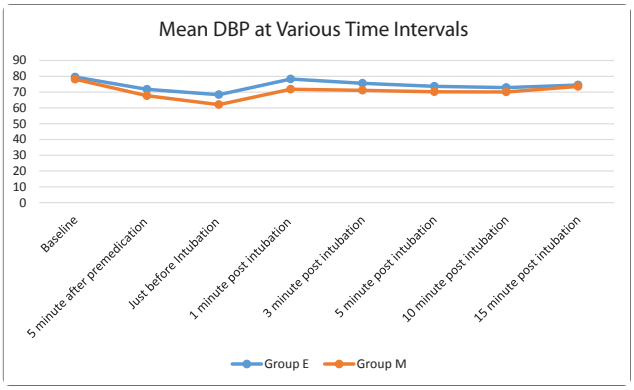

Figure 2: Mean DBP at various time intervals.

DISCUSSION

In our study we found that Esmolol attenuated the increase in heart rate as compared to magnesium sulphate (*p* value < 0.05). This is similar to a study by Korpinen et al & Shroff et al. [9]. There was a statistically significant difference in heart rate between group E and group M after 1 & 3 minutes post intubation. Helfman et al. [10] showed that Esmolol provided consistent & reliable protection against increases in both heart rate and systolic blood pressure accompanying laryngoscopy & intubation. Esmolol according to Jacque et al when administered intravenously 2 minutes before intubation blunted the tachycardia & hypertension for atleast 10 minutes post intubation [11].

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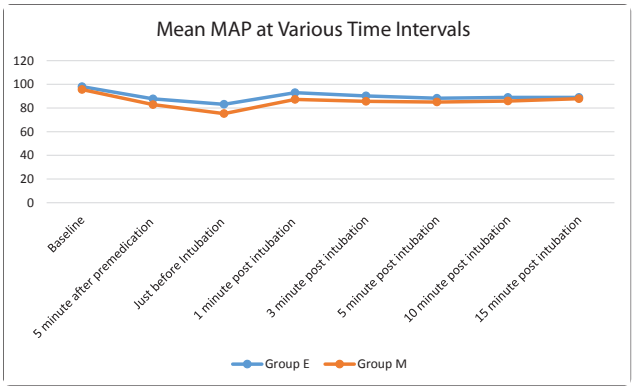

Figure 3: Mean MAP at various time intervals.

Christoph H et al. [12] evaluated the efficacy of intravenous lidocaine and two doses of esmolol for decreasing the cardiovascular response to laryngoscopy & intubation and concluded that esmolol 1-2 mg/ kg is effective in attenuating the heart rate response to tracheal intubation. Neither the two doses of esmolol tested, nor that of lidocaine affected the blood pressure response. Only the combination of lidocaine & esmolol attenuated both heart rate and blood pressure response to tracheal intubation.

Esmolol is effective in the attenuation of the sympathetic response to laryngoscopy & intubation. Bensky et al. [13] suggested that small doses of esmolol 0.2 or 0.4 mg/ kg may block the sympathomimetic effects of laryngoscopy & intubation. Shrestha et al. [14] noted that higher doses of esmolol 1.5 mg/ kg do not completely prevent the pressor & tachycardic response to laryngoscopy & intubation. Samaha et al. [15] have also found a similar effect in addition to ICP.

Heart rate did not decrease after the drug pre- treatment & remained elevated in group M after 3, 5, & 10 minutes post intubation because of the ability of magnesium to inhibit the release of acetylcholine from the vagus nerve [16] resulting in mild increase in heart rate. But after intubation the heart rate did not further increase because prior treatment via infusion decreases the norepinephrine release from the postganglionic sympathetic nerve ending [8,17]. Magnesium causes slight decrease in heart rate because of its effect on S.A node and prolongs the P.R interval [17], which was not seen in our study. In one study intravenous infusion of magnesium decreased the incidence of ventricular arrhythmias in post cardiac surgery patients [18].

Magnesium sulphate provides a good control over rise in systolic blood pressure and diastolic blood pressure in controlled hypertensive patients during tracheal intubation but rise in heart rate is not controlled by it. Esmolol controls both the heart rate and blood pressure its effect in lowering B.P is less as compared to heart rate [19]. Magnesium sulphate causes coronary & systemic vasodilatation which leads to decrease in coronary artery spasm and blood pressure [20]. The decrease in blood pressure is attributed to decrease in sympathetic tone because of sympathetic ganglia blockade [17].

Magnesium administration prior to the induction of anaesthesia in patients with CAD undergoing CABG improved hemodynamics by showing less fluctuation in ST segment and hemodynamic parameters as compared to Lidocaine at the time of endotracheal intubation [21] with a caution in patients on calcium channel blockers, beta blocker and ACE inhibitors.

Both low dose of magnesium (20 mg/kg) and high dose (40 mg/kg) pre-treatment lead to a better hemodynamic profile after endotracheal intubation & sternotomy in patients undergoing CABG surgery [22].

After study drug administration systolic blood pressure decreased in both the groups which was similar to Juhi et al. [23]. Diastolic blood pressure decreased in both the groups. It rose post intubation in both groups but did not reach up to baseline even 15 minutes later, which is similar to Juhi Sharma et al. who observed that both magnesium (40 mg/kg) & Esmolol (1.5 mg/kg) had similar control over systolic blood pressure. The mean arterial pressure decreased in both groups post intubation). G.D Puri et al. [21] concluded that MAP decreased after magnesium sulphate administration alone compared with control group. Our study also shows that magnesium has a fairly good control over blood pressure. It has been shown to inhibit catecholamine release during tracheal intubation [8]. Vasodilatory effects of magnesium are characterized by the decrease in B.P associated with peripheral vasodilatation consistent with increase in cardiac index [21].

In our clinical trial 3 patients in group E had bradycardia as compared to group M. Hypotension was observed in 4 patients in group M as compared to 1 patient in group E. 1 patient complained of pruritis in group M as compared to group E. None of the groups had nausea & vomiting. There were no arrhythmias in any of the group.

Magnesium potentiates the effects of nondepolarising neuromuscular blocking agents [24]. We did not monitor neuromuscular block in these patients to see any potentiation of the paralysis by magnesium sulphate as all the patients were shifted to cardiac surgery ICU intubated for further post-operative ventilation.

A lot of studies have shown various drugs in preventing the pressor response to tracheal intubation, but not the increase in heart rate. Short acting beta blockers like esmolol have the bradycardic, antihypertensive, antiarrhythmic and antiischemic properties. These agents are more effective in preventing the changes in heart rate than the pressor response. They have a place in the cardiac risk patients.

CONCLUSION

Our study results show that Esmolol in an infusion in the dose of 1.5 mg/kg body given 5 minutes before intubation in patients of Rheumatic heart disease undergoing valvular heart replacement provides a smooth induction by an effective control of heart rate and blood pressure which is very much required in such patients as the damaged myocardium will not tolerate the hemodynamic instability during induction of anesthesia. This is the novelty of the study.

We conclude that magnesium sulphate provides a fairly good and sustained control of rise in SBP, DBP & MAP in patients undergoing valvular heart surgery during tracheal intubation, but could not attenuate the rise in heart rate. Esmolol is effective in controlling H.R & B.P. It is an ultra short acting beta blocker with a transient effect & short half life. However its use is not advisable in some patients i.e. asthmatics and patients already having bradycardia which is limited. It is concluded from our study that esmolol controls the hemodynamic response to laryngoscopy and endotracheal intubation better as compared to magnesium sulphate.

We suggest that anaesthetist's desiring a smooth induction for their patients utilize an esmolol infusion 5 minutes before intubation as done in this study.

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